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09/840503

04/23/01

**UTILITY PATENT APPLICATION TRANSMITTAL AND FEE SHEET**

Transmitted herewith for filing under 37 CFR §1.53(b) is the utility patent application of

Applicant (or identifier): IWANOWICZ ET AL.

Title: HETEROCYCLES THAT ARE INHIBITORS OF IMPDH ENZYME

Enclosed are:

1. ☒ Specification (Including Claims and Abstract) - 264 pages
2. ☐ Drawings - sheets
3. ☒ Unexecuted Declaration and Power of Attorney (original or copy)
4. ☐ Microfiche Computer Program (appendix)
5. ☐ Nucleotide and/or Amino Acid Sequence Submission
  - ☐ Computer Readable Copy
  - ☐ Paper Copy
  - ☐ Statement Verifying Identity of Above Copies
6. ☐ Preliminary Amendment
7. ☐ Assignment Papers (Cover Sheet & Document(s))
8. ☐ English Translation of
9. ☐ Information Disclosure Statement
10. ☐ Certified Copy of Priority Document(s)
11. ☒ Return Receipt Postcard
12. ☐ Other:

Filing fee calculation:

- ☐ Before calculating the filing fee, please enter the enclosed Preliminary Amendment.
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Basic Filing Fee							\$	710
Multiple Dependent Claim Fee (\$ 270)							\$	
Foreign Language Surcharge (\$ 130)							\$	
	For	Number Filed		Number Extra		Rate		
Extra Claims	Total Claims	29	-20	9	x	\$ 18 =	\$	162
	Independent Claims	4	-3	1	x	\$ 80 =	\$	80
TOTAL FILING FEE							\$	952

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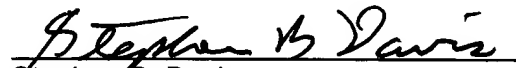
- ☒ Please charge Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company in the amount of \$952. An additional copy of this paper is enclosed. The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.16 and §1.17 which may be required in connection with this application, or credit any overpayment, to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

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Respectfully submitted,



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Date: April 23, 2001

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FOE240-EO504860

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Docket Number QA231

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Box Provisional Patent Application  
Washington, DC 20231

## PROVISIONAL APPLICATION FOR PATENT COVER SHEET

Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

INVENTOR(S)		
Given Name (first and middle (if any))	Family Name or Surname	Residence (City and either State or Foreign Country)
Edwin J Scott H T.G. Murali William J	Iwanowicz Watterson Dhar Pitts	Cranbury, New Jersey Hamilton, New Jersey Newtown, Pennsylvania Newtown, Pennsylvania
TITLE OF THE INVENTION (280 characters max)  HETEROCYCLES THAT ARE INHIBITORS OF IMPDH ENZYME		
CORRESPONDENCE ADDRESS  Direct all correspondence to the address associated with Customer No. 23914, which is currently: Marla J. Mathias Bristol-Myers Squibb Company Patent Department P.O. Box 4000 Princeton, NJ 08543-4000		
ENCLOSED APPLICATION PARTS (check all that apply)  <input checked="" type="checkbox"/> Specification (Including Any Claims and Abstract) - 73 pages <input type="checkbox"/> Drawings - sheets <input type="checkbox"/> Other (specify):		
METHOD OF PAYMENT  The Commissioner is hereby authorized to charge filing fee and any additional fees required to Deposit Account Number: 19-3880 in the name of Bristol-Myers Squibb Company.		
		PROVISIONAL FILING FEE AMOUNT: \$ 150

☐ U.S. Government agency and contract number: (if the invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.)

Respectfully submitted,

Date: April 24, 2000

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provisional has support of the claim.

Heterocycles That Are Inhibitors Of IMPDH Enzyme

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Field of the Invention

The present invention relates to novel compounds which inhibit IMPDH, and to methods of making such compounds. The invention also encompasses pharmaceutical compositions containing these compounds. The compounds and pharmaceutical compositions of the invention are particularly well suited for inhibiting IMPDH enzyme activity and, consequently, can be advantageously used as therapeutic agents for IMPDH-associated disorders. This invention also relates to methods for inhibiting the activity of IMPDH using the compounds of this invention alone or in combination with other pharmaceutically active agents.

20

Background of the Invention

Inosine monophosphate dehydrogenase (IMPDH) has been shown to be a key enzyme in the regulation of cell proliferation and differentiation. Nucleotides are required for cells to divide and replicate. In mammals, nucleotides may be synthesized through one of two pathways: the *de novo* synthesis pathway or the salvage pathway. The extent of utilization of each pathway is dependent on the cell type. This selectivity has ramifications with regard to therapeutic utility as described below.

IMPDH is involved in the *de novo* synthesis of guanosine nucleotides. IMPDH catalyzes the irreversible NAD-dependent oxidation of inosine-5'-monophosphate ("IMP") to xanthosine-5'-monophosphate ("XMP"), Jackson et al., Nature 256:331-333 (1975).

IMPDH is ubiquitous in eukaryotes, bacteria and protozoa. The prokaryotic forms share 30-40% sequence identity with the human enzyme.

Two distinct cDNA's encoding IMPDH have been  
5 identified and isolated. These transcripts are labeled  
type I and type II and are of identical size (514 amino  
acids). Collart et al., J. Biol. Chem. 263:15769-15772  
(1988); Natsumeda et al., J. Biol. Chem. 265:5292-5295  
(1990); and U.S. Patent 5,665,583 to Collart et al.  
10 These isoforms share 84% sequence identity. IMPDH type I  
and type II form tetramers in solution, the enzymatically  
active unit.

B and T-lymphocytes depend on the *de novo*, rather  
than salvage pathway, to generate sufficient levels of  
15 nucleotides necessary to initiate a proliferative  
response to mitogen or antigen. Due to the B and T  
cell's unique reliance on the *de novo* pathway, IMPDH is  
an attractive target for selectively inhibiting the  
immune system without also inhibiting the proliferation  
20 of other cells.

Immunosuppression has been achieved by inhibiting a  
variety of enzymes. Examples include: phosphatase  
calcineurin (inhibited by cyclosporin and FK-506);  
dihydroorotate dehydrogenase (DHODase), an enzyme  
25 involved in the biosynthesis of pyrimidines (inhibited by  
leflunomide and brequinar); the kinase FRAP (inhibited by  
rapamycin); and the heat shock protein hsp70 (inhibited  
by deoxyspergualin).

Inhibitors of IMPDH have also been described in the  
30 art. WO 97/40028 and U.S. Patent 5,807,876 describe a  
class of urea derivatives that possess a common urea  
backbone. WO 98/40381 describes a series of heterocyclic  
substituted anilines as inhibitors of IMPDH.

United States patents 5,380,879 and 5,444,072 and  
35 PCT publications WO 94/01105 and WO 94/12184 describe

mycophenolic acid ("MPA") and some of its derivatives as potent, uncompetitive, reversible inhibitors of human IMPDH type I and type II. MPA has been demonstrated to block the response of B and T-cells to mitogen or antigen. Immunosuppressants, such as MPA and derivatives of MPA, are useful drugs in the treatment of transplant rejection and autoimmune disorders, psoriasis, inflammatory diseases, including, rheumatoid arthritis, tumors and for the treatment of allograft rejection.

These are described in U.S. Pat. Nos. 4,686,234, 4,725,622, 4,727,069, 4,753,935, 4,786,637, 4,808,592, 4,861,776, 4,868,153, 4,948,793, 4,952,579, 4,959,387, 4,992,467, and 5,247,083.

Tiazofurin, ribavirin and mizoribine also inhibit IMPDH. These nucleoside analogs are competitive inhibitors of IMPDH, however these agents inhibit other NAD dependent enzymes. This low level of selectivity for IMPDH limits the therapeutic application of tiazofurin, ribavirin and mizoribine. Thus, new agents which have improved selectivity for IMPDH would represent a significant improvement over the nucleoside analogs.

Mycophenolate mofetil, sold under the trade name CELLCEPT, is a prodrug which liberates MPA *in vivo*. It is approved for use in preventing acute renal allograft rejection following kidney transplantation. The side effect profile limits the therapeutic potential of this drug. MPA is rapidly metabolized to the inactive glucuronide *in vivo*. In humans, the blood levels of glucuronide exceed that of MPA. The glucuronide undergoes enterohepatic recycling causing accumulation of MPA in the bile and subsequently in the gastrointestinal tract. This together with the production of the inactive glucuronide effectively lowers the drug's *in vivo* potency, while increasing its undesirable gastrointestinal side effects.

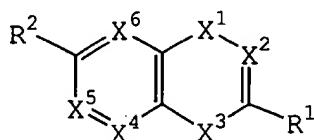
Unlike type I, type II mRNA is preferentially upregulated in human leukemic cell lines K562 and HL-60. Weber, J. Biol. Chem. 266: 506-509 (1991). In addition, cells from human ovarian tumors and leukemic cells from patients with chronic granulocytic, lymphocytic and acute myeloid leukemias also display an up regulation type II mRNA. This disproportionate increase in IMPDH activity in malignant cells may be addressed through the use of an appropriate IMPDH inhibitor. IMPDH has also been shown to play a role in the proliferation of smooth muscle cells, indicating that inhibitors of IMPDH may be useful in preventing restenosis or other hyperproliferative vascular diseases.

IMPDH has been shown to play a role in viral replication in some viral cell lines. Carr, J. Biol. Chem. 268:27286-27290 (1993). The IMPDH inhibitor VX-497, is currently being evaluated for the treatment of hepatitis C virus in humans. Ribavirin has also been used in the treatment of hepatitis C and B viruses and when used in combination with interferon an enhancement in activity was observed. The IMPDH inhibitor ribavirin is limited by its lack of a sustained response in monotherapy and broad cellular toxicity.

There remains a need for potent selective inhibitors of IMPDH with improved pharmacological properties, physical properties and fewer side effects. Such inhibitors would have therapeutic potential as immunosuppressants, anti-cancer agents, anti-vascular hyperproliferative agents, antiinflammatory agents, antifungal agents, antipsoriatic and anti-viral agents. The compounds of the present invention are effective inhibitors of IMPDH.

Summary of the Invention

The present invention provides heterocyclic compounds of the following formula (I), their  
 5 enantiomers, diastereomers, tautomers and pharmaceutically acceptable salts, prodrugs and solvates thereof, for use as IMPDH inhibitors:



(I)

10

wherein:

X<sup>1</sup> is C=O, -S(O)-, or -S(O)<sub>2</sub>-.

X<sup>2</sup> is CR<sup>3</sup> or N.

X<sup>3</sup> is -NH-, -O-, or -S-.

15

X<sup>4</sup> is CR<sup>4</sup> or N.

X<sup>5</sup> is CR<sup>5</sup> or N.

X<sup>6</sup> is CR<sup>6</sup> or N.

R<sup>1</sup> is alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycloalkyl, or heteroaryl.

20

R<sup>2</sup> is halogen, cyano, nitro, hydroxy, oxo (double bond is no longer present between CR<sup>2</sup> and X<sup>6</sup>), SR<sup>7</sup>, S(O)R<sup>7</sup>, SO<sub>2</sub>R<sup>7</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, CO<sub>2</sub>R<sup>7</sup>, C(O)NR<sup>8</sup>R<sup>9</sup>, or heteroaryl.

25

R<sup>3</sup> is hydrogen, halogen, cyano, CO<sub>2</sub>R<sup>7</sup>, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl, substituted alkynyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycloalkyl or heteroaryl.

R<sup>4</sup>, R<sup>5</sup>, and R<sup>6</sup> are independently selected from the  
 30 group consisting of hydrogen, halogen, nitro, cyano,



O-R<sup>7</sup>, NR<sup>8</sup>R<sup>9</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO<sub>2</sub>R<sup>7</sup>, SO<sub>3</sub>R<sup>7</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, CO<sub>2</sub>R<sup>7</sup>, C(O)NR<sup>8</sup>R<sup>9</sup>, C(O)alkyl, C(O)substituted alkyl, alkyl, substituted alkyl, alkenyl, substituted alkenyl, alkynyl and substituted alkynyl.

- 5 R<sup>7</sup>, R<sup>10</sup>, and R<sup>11</sup>, are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, cycloalkyl, substituted cycloalkyl, C(O)alkyl, C(O)substituted alkyl, C(O)cycloalkyl, C(O)substituted cycloalkyl, C(O)aryl, C(O)substituted aryl, 10 C(O)Oalkyl, C(O)Osubstituted alkyl, C(O)heterocycloalkyl, C(O)heteroaryl, aryl, substituted aryl, heterocycloalkyl and heteroaryl.

- R<sup>8</sup> and R<sup>9</sup> are independently selected from the group consisting of hydrogen, alkyl, substituted alkyl, 15 cycloalkyl, substituted cycloalkyl, alkenyl, alkynyl, C(O)alkyl, C(O)substituted alkyl, C(O)cycloalkyl, C(O)substituted cycloalkyl, C(O)aryl, C(O)substituted aryl, C(O)Oalkyl, C(O)Osubstituted alkyl, C(O)heterocycloalkyl, C(O)heteroaryl, aryl, substituted 20 aryl, heterocycloalkyl, and heteroaryl or R<sup>8</sup> and R<sup>9</sup> taken together with the nitrogen atom to which they are attached complete a heterocycloalkyl or heteroaryl ring.

- R<sup>3</sup> and R<sup>1</sup> may be taken together with the carbon atoms to which they are attached to form a monocyclic or 25 substituted monocyclic ring system of 5 or 6 carbon atoms.

R<sup>4</sup> and R<sup>5</sup> may be joined together by the chain -O-CH<sub>2</sub>-O- or -O-CH<sub>2</sub>-CH<sub>2</sub>-O- .

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Detailed Description Of The Invention

The following are definitions of the terms as used throughout this specification and claims. The initial  
 5 definition provided for a group or term herein applies to that group or term throughout the present specification, individually or as part of another group, unless otherwise indicated.

The term "alkyl" refers to straight or branched  
 10 chain hydrocarbon groups having 1 to 12 carbons atoms, preferably 1 to 8 carbon atoms, and most preferably 1 to 4 carbon atoms.

The term "substituted alkyl" refers to an alkyl group as defined above having one, two, or three substituents  
 15 selected from the group consisting of halo, cyano,  $O-R^7$ ,  $S-R^7$ ,  $NR^8R^9$ , nitro, cycloalkyl, substituted cycloalkyl, oxo, aryl, substituted aryl, heterocycloalkyl, heteroaryl,  $CO_2R^7$ ,  $S(O)R^7$ ,  $SO_2R^7$ ,  $SO_3R^7$ ,  $SO_2NR^8R^9$ ,  $C(O)NR^8R^9$ ,  $C(O)alkyl$ , and  $C(O)H$ .

20 The term "alkenyl" refers to straight or branched chain hydrocarbon groups having 2 to 12 carbon atoms and one, two or three double bonds, preferably 2 to 6 carbon atoms and one double bond.

The term "substituted alkenyl" refers to an alkenyl  
 25 group as defined above having one, two, or three substituents selected from the group consisting of halo, cyano,  $O-R^7$ ,  $S-R^7$ ,  $NR^8R^9$ , nitro, cycloalkyl, substituted cycloalkyl, oxo, aryl, substituted aryl, heterocycloalkyl, heteroaryl,  $CO_2R^7$ ,  $S(O)R^7$ ,  $SO_2R^7$ ,  $SO_3R^7$ ,  
 30  $SO_2NR^8R^9$ ,  $C(O)NR^8R^9$ ,  $C(O)alkyl$ , and  $C(O)H$ .

The term "alkynyl" refers to straight or branched chain hydrocarbon group having 2 to 12 carbon atoms and one, two or three triple bonds, preferably 2 to 6 carbon atoms and one triple bond.

The term "substituted alkynyl" refers to an alkynyl group as defined above having one, two or three substituents selected from the group consisting of halo, cyano,  $O-R^7$ ,  $S-R^7$ ,  $NR^8R^9$ , nitro, cycloalkyl, substituted cycloalkyl, oxo, aryl, substituted aryl,

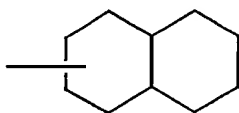
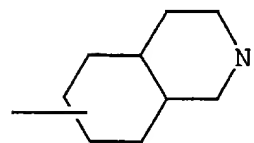
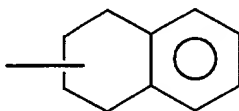
5 cycloalkyl, oxo, aryl, substituted aryl, heterocycloalkyl, heteroaryl,  $CO_2R^7$ ,  $S(O)R^7$ ,  $SO_2R^7$ ,  $SO_3R^7$ ,  $SO_2NR^8R^9$ ,  $C(O)NR^8R^9$ ,  $C(O)alkyl$ , and  $C(O)H$ .

The term "halo" refers to chloro, bromo, fluoro, and iodo.

10 The term "cycloalkyl" refers to fully saturated and partially unsaturated monocyclic hydrocarbon rings of 3 to 9, preferably 3 to 7 carbon atoms. Also included in this definition are bicyclic rings where the cycloalkyl ring as defined above has a fused aryl, substituted aryl,

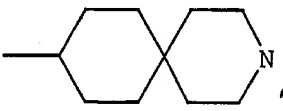
15 cycloalkyl, substituted cycloalkyl, heterocycloalkyl, or heteroaryl ring provided that the point of attachment is

in the cycloalkyl ring, i.e.



etc., as well as a

20 cycloalkyl ring as defined above having a two or three carbon bridge or a spirocycloalkyl in which a carbon atom of the cycloalkyl ring has a carbon atom in common with a second cycloalkyl, substituted cycloalkyl, or heterocycloalkyl ring again provided that the point of attachment is in the cycloalkyl ring, i.e.



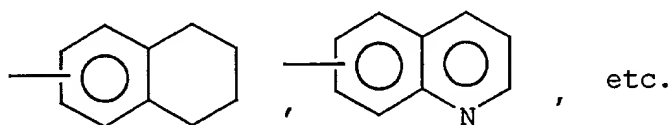
etc,

25

The term "substituted cycloalkyl" refers to such cycloalkyl group as defined above having one, two or

- three substituents selected form the group consisting of halogen, nitro, alkyl, substituted alkyl, alkenyl, cyano, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, heterocycloalkyl, heteroaryl, oxo, OR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>,  
 5 C(O)NR<sup>8</sup>R<sup>9</sup>, OC(O)R<sup>7</sup>, OC(O)OR<sup>7</sup>, OC(O)NR<sup>8</sup>R<sup>9</sup>, OCH<sub>2</sub>CO<sub>2</sub>R<sup>7</sup>, C(O)R<sup>7</sup>, NR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>C(O)R<sup>7</sup>, NR<sup>10</sup>C(O)OR<sup>7</sup>, NR<sup>10</sup>C(O)C(O)OR<sup>7</sup>, NR<sup>10</sup>C(O)C(O)NR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>C(O)C(O)alkyl, NR<sup>10</sup>C(NCN)OR<sup>7</sup>, NR<sup>10</sup>C(O)NR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>C(NCN)NR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>C(NR<sup>11</sup>)NR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>SO<sub>2</sub>R<sup>7</sup>, SR<sup>7</sup>, S(O)R<sup>7</sup>, SO<sub>2</sub>R<sup>7</sup>, SO<sub>3</sub>R<sup>7</sup>, SO<sub>2</sub>NR<sup>8</sup>R<sup>9</sup>, NHOR<sup>7</sup>,  
 10 NR<sup>10</sup>NR<sup>8</sup>R<sup>9</sup>, N(COR<sup>7</sup>)OR<sup>10</sup>, N(CO<sub>2</sub>R<sup>7</sup>)OR<sup>10</sup>, C(O)NR<sup>10</sup>(CR<sup>12</sup>R<sup>13</sup>)<sub>r</sub>R<sup>7</sup>, CO(CR<sup>12</sup>R<sup>13</sup>)PO(CR<sup>14</sup>R<sup>15</sup>)qCO<sub>2</sub>R<sup>7</sup>, CO(CR<sup>12</sup>R<sup>13</sup>)rOR<sup>7</sup>, CO(CR<sup>12</sup>R<sup>13</sup>)PO(CR<sup>14</sup>R<sup>15</sup>)qR<sup>7</sup>, CO(CR<sup>12</sup>R<sup>13</sup>)rNR<sup>8</sup>R<sup>9</sup>, OC(O)O(CR<sup>12</sup>R<sup>13</sup>)mNR<sup>8</sup>R<sup>9</sup>, OC(O)N(CR<sup>12</sup>R<sup>13</sup>)rR<sup>7</sup>, O(CR<sup>12</sup>R<sup>13</sup>)mNR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>C(O)(CR<sup>12</sup>R<sup>13</sup>)rR<sup>7</sup>, NR<sup>10</sup>C(O)(CR<sup>12</sup>R<sup>13</sup>)rOR<sup>7</sup>,  
 15 NR<sup>10</sup>C(=NC)(CR<sup>12</sup>R<sup>13</sup>)rR<sup>7</sup>, NR<sup>10</sup>CO(CR<sup>12</sup>R<sup>13</sup>)rNR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>(CR<sup>12</sup>R<sup>13</sup>)mOR<sup>7</sup>, NR<sup>10</sup>(CR<sup>12</sup>R<sup>13</sup>)rCO<sub>2</sub>R<sup>7</sup>, NR<sup>10</sup>(CR<sup>12</sup>R<sup>13</sup>)mNR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>(CR<sup>12</sup>R<sup>13</sup>)nSO<sub>2</sub>(CR<sup>14</sup>R<sup>15</sup>)qR<sup>7</sup>, CONR<sup>10</sup>(CR<sup>12</sup>R<sup>13</sup>)nSO<sub>2</sub>(CR<sup>14</sup>R<sup>15</sup>)qR<sup>7</sup>, SO<sub>2</sub>NR<sup>10</sup>(CR<sup>12</sup>R<sup>13</sup>)nCO(CR<sup>14</sup>R<sup>15</sup>)qR<sup>7</sup>, and SO<sub>2</sub>NR<sup>10</sup>(CR<sup>12</sup>R<sup>13</sup>)mOR<sup>7</sup>.

- The term "aryl" refers to the phenyl, 1-naphthyl,  
 20 and 2-naphthyl, preferably phenyl, as well as an aryl ring having a fused cycloalkyl, substituted cycloalkyl, heterocycloalkyl, or heteroaryl ring provided that the point of attachment is in the aryl ring, i.e.



- 25 The term "substituted aryl" refers to such aryl groups as defined above having one, two, or three substituents selected form the group consisting of halogen, nitro, alkyl, substituted alkyl, alkenyl, cyano, cycloalkyl, substituted cycloalkyl, aryl, substituted  
 30 aryl, heterocycloalkyl, heteroaryl, OR<sup>7</sup>, CO<sub>2</sub>R<sup>7</sup>, C(O)NR<sup>8</sup>R<sup>9</sup>, OC(O)R<sup>7</sup>, OC(O)OR<sup>7</sup>, OC(O)NR<sup>8</sup>R<sup>9</sup>, OCH<sub>2</sub>CO<sub>2</sub>R<sup>7</sup>, C(O)R<sup>7</sup>, NR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>C(O)R<sup>7</sup>, NR<sup>10</sup>C(O)OR<sup>7</sup>, NR<sup>10</sup>C(O)C(O)OR<sup>7</sup>, NR<sup>10</sup>C(O)C(O)NR<sup>8</sup>R<sup>9</sup>, NR<sup>10</sup>C(O)C(O)alkyl, NR<sup>10</sup>C(NCN)OR<sup>7</sup>, NR<sup>10</sup>C(O)NR<sup>8</sup>R<sup>9</sup>,